ORIGINAL ARTICLE

Normalisation of the International Normalised Ratio (INR) Prior to Interventional Procedure: Is it Necessary?

Mohd Tarmizi Mohamad Mahyedin[1], Afifah Hassan[2], Abdul Rahim Hussein[1]

[1] Institut Perubatan dan Pergigian Termaju, Universiti Sains Malaysia, Bertam, 13200 Kepala Batas, Pulau Pinang, Malaysia
[2] Pusat Darah Negara, 50400 Kuala Lumpur, Wilayah Persekutuan Kuala Lumpur, Malaysia

ABSTRACT

Introduction: The fresh frozen plasma (FFP) is frequently prescribed either for therapeutic or prophylactic transfusion. The international normalised ratio (INR) value of 1.50 and above is frequently reported to be a transfusion trigger for FFP prior to interventional procedure. This study aimed to evaluate the efficacy of prophylactic FFP transfusion in normalising the INR and to determine the post-transfusion outcomes. **Methods:** A prospective cross-sectional study involved 81 patients who received prophylactic FFP transfusion over a period of three months. All demographic, clinical data and outcomes of FFP transfusion were captured and filled in the research proforma. **Results:** The proportion of patients achieved posttransfusion INR below 1.51 was 30.30% (n=27). The majority of patients underwent the interventional procedures with posttransfusion INR > 1.50 (n=52) without experiencing any bleeding episodes. Overall, FFP transfusion resulted in significant median INR difference from 1.89 (IQR, 0.53) to 1.60 (IQR, 0.25); p< 0.001. The greater median INR difference was observed in group with pretransfusion INR > 2.00 and who received FFP doses between 10.00 to 20.00 ml kg-1 (p < 0.001). The INR difference showed the significant, positive correlation with pretransfusion INR values (rs= 0.83, p < 0.001) and FFP doses (rs= 0.72, p< 0.001). **Conclusions:** The interventional procedures were safely carried out despite abnormal posttransfusion INR. The prophylactic FFP transfusions could be avoided in patients with mild coagulopathy (INR 1.50 - 2.00) prior interventional procedures.

Keywords: Prophylactic FFP transfusion, Interventional procedures, International normalised ratio, FFP doses, Coagulopathy

Corresponding Author:
Abdul Rahim Hussein, MBBS MPath, PhD
Email: drrahim@usm.my
Tel: +604-5622556

INTRODUCTION

The usage of fresh frozen plasma (FFP) has grown steadily over past two decades in the worldwide. Prophylactic FFP transfusion accounts for almost 50% and was given prior an invasive procedure or surgery (1). FFP transfusion was prescribed by clinicians as either for therapeutic or prophylactic transfusion (2, 3). FFP is known to be effective in correcting multiple coagulation factor deficiencies such as in massive bleeding due to trauma and disseminated intravascular coagulation (DIC) due to many causes. In certain circumstances, FFP is also transfused to non-bleeding patients with coagulopathy to minimise the risk of bleeding as frequently seen in critically ill patients (4).INR is commonly used to assess coagulopathy (5). Multiple international guidelines proposed the FFP transfusion can be considered prior to invasive procedure or surgery in patient with clinical coagulopathy. The cut off value for FFP transfusion was PT greater than 1.5 times the midpoint of the normal range (usually >18 seconds or INR 1.5) or activated Partial Thromboplastin Time (aPTT) greater than 1.5 times the top of the normal range (6-9).

The efficacy of FFP transfusion on INR normalisation varied widely, ranged from 0.8% to 54% had a corrected INR less than 1.50 (10-12). FFP dose is depends on the clinical situation and coagulation parameters. There was an association between the volume and doses of FFP with reduction values of posttransfusion INR. Higher median dose of FFP was infused to achieved posttransfusion INR < 1.50 (2, 12). FFP dose < 10 ml kg-1 was unlikely to correct coagulation factor defects (13).Bleeding is a common complication during and after any interventional procedure. Numerous retrospective studies reported the low incidence (<1%) of major bleeding after an invasive procedure in patients with a prolonged INR (14-19). Bleeding complications post procedure did not differ between transfused vs non-transfused patients, p= 0.77 (10). There was evidence that the adverse risk for prophylactic FFP transfusion may outweigh its clinical benefit, especially when the blood component was infused in haemodynamically stable patients with minimal prolongation of PT or INR

(3, 20, 21).

The aim of this study was to evaluate the efficacy of FFP transfusions in normalising the INR prior to interventional procedures and to determine the post transfusion outcomes (INR difference, bleeding episode and adverse transfusion reaction). Apart from that, to establish the relationship between INR difference with different groups of pretransfusion INR values and FFP doses. Hence, it will provide an evidence-based transfusion medicine in relation with prophylactic FFP transfusion specifically prior to interventional procedures.

MATERIALS AND METHODS

Study design

This prospective cross-sectional study was composed of data from 81 patients who received FFP transfusions prior to interventional procedures within the data collection period. This study was conducted at both Pusat Darah Negara (PDN) and Hospital Kuala Lumpur (HKL). The period of study was from 1st June 2016 until 31st March 2017. The period of data collection started from December 2016 to February 2017. The inclusion criteria includingpatient (12 years old and above) with coagulopathy (INR value above 1.50), received prophylactic FFP transfusion and undergoing interventional procedure. Pre transfusion (within 24 hours before the FFP transfusion) and post transfusion (within 24 hours after completion of FFP infusion) laboratory tests were taken. Any FFP transfusion dose prior to the procedure was counted for data analysis.

Statistical analysis

Two independent variables were included for statistical analysis; the pretransfusion INR value and the dose of FFP transfusion. The data of pretransfusion INR values were divided into two groups for further data analysis. The first group was with INR values that ranged from 1.51 to 2.00 (mild coagulopathy) and the second group with INR above 2.00. For analysis, the doses of FFP transfusions were divided into two groups:

i) The first group received FFP dose of less than 10.00 ml kg^{-1}

ii) Second group received FFP dose from 10.00 to 20.00 ml kg^{-1} FFP (recommended doses for FFP transfusion).

The INR difference was dependent variable measured. The INR difference was a difference between the pretransfusion INR value and posttransfusion INR value. The statistical analysis was performed using SPSS version 24.0 for Windows (SPSS, Chicago Illinois, USA) to present the descriptive, statistical and univariate analysis. Numbers, percentages, means and medians were used in the descriptive analysis. For the statistical analysis, the Mann Whitney U-test was used for qualitative data with the median. Meanwhile, the Wilcoxon Signed-Ranked test and Spearman's correlation coefficient tests were used for numerical data analysis. The level of significance was set at p value of 0.05.

RESULTS

The majority of the patients were male with 69.1%. The mean ages for all patients were 56.63 ± 15.30 years old. Ten types of interventional procedures were recorded with the three highest number of interventional procedures performed were paracentesis (18), internal jugular vein cannulation (18) and femoral vein cannulation (15). The majority of patients were warded under medical department (70.37%), followed by neurosurgery (9.87%), general surgery (7.41%) and orthopaedic surgery (7.41%). The total FFP transfused were 291 units with a mean of 3.6 ± 1.15 units for each patient. More than half of the patients (54.32%) recorded pretransfusion of INR values of 2.00 and below. The overall median FFP dose infused was 11.20 ml kg^{-1} (IQR, 5.15) for each patient. Nearly two-thirds of the patients (62.96%) were infused with FFP doses ranging from 10.00 to 20.00 ml kg^{-1} (Table I).

Table I: Characteristics distribution of the patients (n = 81)

Characteristics	Frequency (%)	Mean (SD)	Median (IQR)
Gender			
Male	56 (69.14)		
Female	25 (30.86)		
Age (years)		56.63 ± 15.30	
Interventional Procedure			
Paracentesis	18 (22.22)		
Internal Jugular Vein Cannulation	18 (22.22)		
Femoral Vein Cannulation	15 (18.52)		
Thoracocentesis	9 (11.11)		
OGDS	7 (8.64)		
Collection incision and drainage	4 (4.94)		
ERCP	4 (4.94)		
Colonoscopy	3 (3.70)		
Organ biopsy	2 (2.47)		
Lumbar puncture	1 (1.23)		
Department			
Medical	57 (70.37)		
Neurosurgery	8 (9.87)		
General Surgery	6 (7.41)		
Orthopaedic Surgery	6 (7.41)		
Oncology	2 (2.47)		
Urology	2 (2.47)		
FFP	291 Units	3.61 ± 1.15	
Pre transfusion INR value			
1.51-2.00	44 (54.32)		
2.01-5.00	37 (45.68)		
FFP dose (ml kg^{-1})			11.20 (5.15)
< 10.00	30 (37.04)		
10.00 to 20.00	51 (62.96)		

Outcomes: laboratory parameters and clinical status

The percentage of patients with posttransfusion INR values of 1.50 and below was 33.30%. This includes a patient with recorded posttransfusion INR normalised to 1.18. The overall median of INR difference was 0.38 (IQR, 0.43). The rate of bleeding episodes were 2.50% with one patient developing major bleeding (posttransfusion INR 1.51) and one patient experienced minor bleeding (posttransfusion INR 1.65). Two patients (2.50%) experienced transfusion reaction episodes within the study period (Table II).

Table II: Outcomes of FFP transfusion (n=81)

Characteristics	Frequency (%)	Median (IQR)
Posttransfusion INR value		
≤1.50	27 (33.30)	
1.51 - 2.00	47 (58.00)	
2.01 - 3.00	7 (8.70)	
INR difference (pre INR minus post INR)		0.38 (0.43)
Bleeding outcome		
No bleeding	79 (97.50)	
Minor bleeding	1 (1.25)	
Major bleeding	1 (1.25)	
Adverse transfusion reaction		
No transfusion reaction	79 (97.50)	
Transfusion reaction	2 (2.50)	

Efficacy of FFP transfusion (n = 81)

FFP transfusion resulted in a median difference of INR from 1.89 (IQR, 0.59) to 1.60 (IQR, 0.25); p< 0.001.

INR difference and groups of pretransfusion INR value

Patients with pretransfusion INR values of above 2.00 have significantly higher median INR differences (0.63, IQR 0.70) compared to the patients with pretransfusion INR values of 1.51 to 2.00 (0.21, IQR 0.21) (Table III).

INR difference and groups of FFP dose

Patients who received FFP doses from 10.00 to 20.00 ml kg-1 have a significantly higher median INR difference (0.57, IQR 0.33) compared to the patients who received FFP doses of less than 10.00 ml kg-1 (0.17, IQR 0.16) (Table III).

Table III: Comparison of median INR difference between pretransfusion INR groups and FFP dose groups

Parameter	N (%)	Median INR difference (IQR)	Z stat[b]	P value
Pre transfusion INR groups				
1.51-2.00	44 (54.32)	0.21 (0.21)	-6.851	<0.001
2.01-5.00	37 (45.68)	0.63 (0.70)		
FFP dose groups (ml kg^{-1})				
< 10.00	30 (37.04)	0.17 (0.16)	-6.251	<0.001
10.00 to 20.00	51 (62.96)	0.57 (0.33)		

[b]Mann-Whitney test

Correlation between pretransfusion INR value and INR difference

Overall, there was a significant, positive and excellent correlation between the pretransfusion INR values and INR differences, rs = 0.83, p < 0.001. The high pretransfusion INR value correlated with the increase in INR difference (Figure 1).

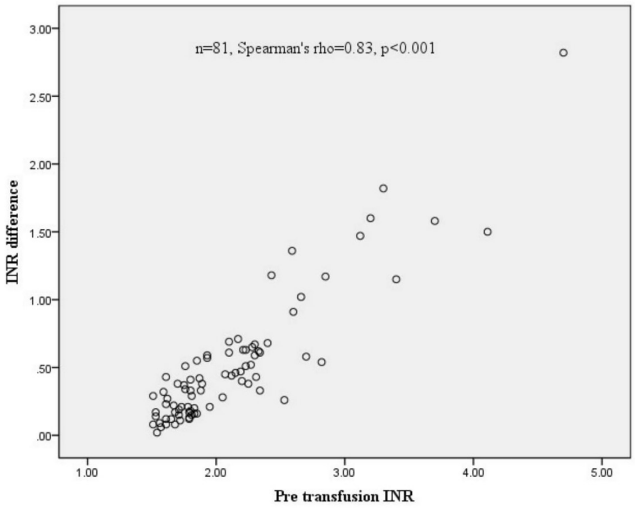

Figure 1: Scartterplot graph of relationship between pretransfusion INR value and INR difference

Correlation between FFP dose and INR difference

Overall, there was a significant, positive and good correlation between FFP doses and INR differences, rs = 0.72, p< 0.001. The increase of FFP doses correlated with the increase in INR difference (Figure 2).

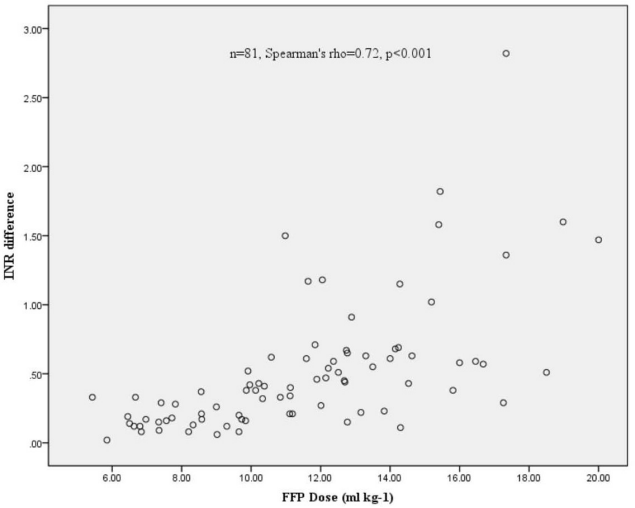

Figure 2: Scartterplot graph of relationship between FFP dose and INR difference

DISCUSSION

The clinical use of FFP has expanded for prophylactic transfusion starting from the last decade. However, there are concerns about the effects of FFP to preventing bleeding episodes. Despite the lack of supportive evidences, prophylactic FFP is often transfused into haemodynamically stable patients (non-bleeding) with elevated INR prior to the invasive procedures (20). A few RCT studies found the prophylactic FFP transfusions were given to correct coagulopathy before an invasive procedures such as thoracocentesis, central vein cannulations and percutaneous tracheotomy (10, 22). Moreover, numerous retrospective studies reported that the risk of bleeding after an invasive procedure is low and the majority of bleeding cases did not require blood transfusions (19, 20, 23).

This current study revealed that there was 62.96% (51) of patients infused with FFP doses from 10.00 to 20.00 ml kg-1 and another 30 patients were transfused with doses lower than the recommended FFP dose. Multiple guidelines or previous studies recommended that the therapeutic doses for FFP infusions are 10.00 to 15.00 ml kg-1 body weight. The dose of FFP depends on the clinical situation and laboratory parameters. These factors may justify the administration of higher doses (24-28).

In the current study, INR values of above 1.50 were chosen in line with current clinical practice and it has been reported to be a minimal value for FFP transfusion (2, 5, 6, 10, 13, 29). FFP transfusions resulted in a reduction of posttransfusion INR in all study subjects. However, the proportion of patients who have achieved posttransfusion INR values of below 1.51 was only 33.30% (27 patients). The current study proportion was smaller as compared to the RCT study by Muller et al. (2015), was reported around 54% of 38 patients achieved INR corrections of less than 1.508. The study subjects with pretransfusion INR ranging from 1.50 until 3.00 were included in that study. However, for the current study, the highest pretransfusion INR value was 4.11. Two previous retrospective study on effectiveness of FFP transfusion showed 1% and 36% of patient achieved INR corrected less than 1.50 respectively (11, 12). Forty-four patients recorded pretransfusion INR values ranging from 1.51 to 2.00 (mild coagulopathy) with 23 patients documenting posttransfusion INR values of more than 1.50 (uncorrected). In line with most studies, it has shown a reduction but failed to achieve complete normalisation of INR after FFP transfusions (11, 12, 27, 30). This is probably due to a low FFP dose infused and the majority of cases with minimally elevated pretransfusion INR (28, 31).

The level of coagulation factor ranged from 30% to 40% was often needed for haemostasis (32) and levels are equivalent to INR values between 1.50 to 2.00 (33). The incidence of major bleeding reported to be less than 1% after an invasive procedure in coagulopathy patients (14-16). However, in the current study, the rate of minor bleeding episodes was 1.25% (one case). Majority of bleeding cases did not require blood transfusions (17, 18, 22) and could be safely carried out without prophylactic FFP transfusions (10, 34, 35). The patient presented with oozing of blood from the femoral catheter insertion site. The repeated INR value was 1.65 prior to cannulation and the oozing was well controlled by applying local pressure over the insertion site. Meanwhile, one case reported having anterior abdominal wall haematoma (major bleeding episode) after undergoing peritoneal tapping (paracentesis) with INR value of 1.51 post-FFP transfusion. Interestingly, a majority of the patients underwent the interventional procedure with posttransfusion INR above 1.50 (52 patients) without any bleeding episodes documented. The findings suggested that the interventional procedures could be feasible and safely carried out without a complete normalisation of INR, especially in patients with mild coagulopathy (INR < 2.00) with proper and good skilled procedure techniques by the clinician.

Transfusion of any blood components is not without its complications. There were two patients reported to have acute transfusion reactions. In both cases, the severity was mild without any morbidity and they were managed symptomatically. This reaction is caused by recipient antibodies being against HLA determinants on transfused leucocytes in plasma while the dermal reactions are caused by sensitivity to foreign plasma proteins. Destruction of white blood cells during freeze thaw can release bioactive mediators that may mediate FNHTR (36).

Dzik W.H. (2004) described the exponential association between coagulation protein levels and coagulation parameters. The degree of INR normalisation post FFP transfusions was correlated with the magnitude of the pretransfusion INR abnormalities. A small increase in the concentration of coagulation proteins will have a larger impact on the posttransfusion INR in recipient with markedly prolonged INR. However, with the similar concentration of proteins will have a small effect on mildly elevated pretransfusion INR. The normalisation of mild elevation of INR often requires larger volume of FFP infusion. The curve as a reference and will vary for each individual patient (33).

There was significant INR difference based on pretransfusion INR values and FFP doses given. Overall, patients with pretransfusion INR values of more than 2.00 reported having higher median INR difference (0.63, IQR 0.70) compared to pretransfusion INR of 1.51 to 2.00. These findings were coherent with previous studies on the effects of FFP transfusion on INR difference. There was significant, greater improvement of INR difference with the higher pretransfusion INR

values (2, 37) and minimally effective in correcting mildly elevated INR (10, 28, 38). Sezik et al. (2014) retrospectively studied the effect of FFP transfusion on INR in an emergency setting. Eighty-seven patients included for study and then were categorised based on severity of pretransfusion coagulation test abnormalities for data analysis. They reported the significant, greater improvement of INR difference for FFP transfusion with the higher pretransfusion INR values (mean INR difference was 0.05 ± 0.30 for pretransfusion INR values of less than 2.00 and 1.45 ± 0.80 for those between 2.00 and 5.00, $p < 0.001$). The authors suggested the pretransfusion INR values should be counted for FFP dosing calculation prior to transfusions (37). Holland and Brooks, 2006 however, found a linear relationship between reduction of INR and the pretransfusion INR values for adult patients. The significant amount of INR difference was expected in patients with pretransfusion INR of more than 2.00. FFP transfusions were minimally effective in correcting mild elevations in INR < 1.70 (28). The transfusion of FFP will have little effect on minimally elevated INRs due to small differences in coagulation activity between FFP and the patient's plasma. One or 2 units of FFP (225-450 mL) would increase the coagulation factor levels by 7.5% and 15% in a 70 kg recipient, respectively. However, the significant INR difference was not expected to achieve in modestly elevated INR. FFP will only affect the INR when there is a relatively large difference between the coagulation activity of the FFP and the patient's plasma. The transfusion of FFP will have insignificant effect on mild elevated INRs due to small differences in coagulation proteins between donor and the patient's plasma (31).

The INR difference was significant and correlated with the pretransfusion INR values ($rs = 0.83$, $p < 0.001$). The RCT study conducted by Muller et al. (2015) found a good correlation ($r = 0.68$, $p< 0.01$) between INR reduction values and pretransfusion INR levels among 38 patients who underwent the multiple invasive procedures. They concluded that patients with higher pretransfusion INR values documented the greatest reduction of INR after FFP infusion (10).
Other studies reported a similar good relationship of median reductions in INR with pretransfusion INR value. Shinagare et al. (2010) also have found a linear relationship ($r = 0.89$) between INR difference per unit of FFP and pretransfusion INR values (39). A recent study by Akinchi et al. (2016) reported a strong positive correlation ($r = 0.85$) between INR difference and elevated pre-transfusion INRs in 32 patients admitted to emergency department (40).

The recommended therapeutic dose of FFP is 10.00-15.00 ml kg-1 of body weight. However, it depends on the clinical conditions and abnormalities laboratory parameters (21, 24, 25, 41), which may indicated to administrate the higher doses of FFP (28, 31, 42). The majority of patients (51 out of 81 cases) received FFP transfusion within the recommended FFP dose (10.00 to 20.00 ml kg-1) and 37.25% (19 patients) of them achieved posttransfusion INR values of 1.50 and below. As expected, the comparison of both groups showed that the group with the FFP dosing of 10.00 to 20.00 ml kg-1 documented a significantly higher median INR difference (0.57, IQR 0.33). The median of INR difference was reported to be higher in the group with pretransfusion INR of more than 2.00 (0.65, IQR 0.65). From the results above, the normalisation posttransfusion INR value of less than 1.50 is achievable provided patients were infused with an adequate FFP dose (with sufficient coagulation proteins). The increased FFP dose given has a significant correlation with the increase in INR difference, $rs= 0.72$, $p< 0.001$.

The current findings were in line with the study conducted by Chowdhury et al. in 2004. They compared the effects of FFP transfusion between the recommended FFP doses (given according to established guidelines) with higher FFP doses given in critically ill patients. Ten patients were given median FFP dose of 12.30 ml kg-1 and 12 patients received median FFP dose of 33.50 ml kg-1. The higher FFP dose was required to elevate the coagulation proteins to more than 30 IU/L. The efficacy of FFP was greater with a dose of 30.00 ml kg-1 to correct INR with adequate individual coagulation factors (10). Recently, Muller et al. (2015) reported more successful outcomes whereby more than half (54%) of the patients had corrected INR values of below 1.50 after receiving a fixed FFP dose of 12.00 ml kg-1 (27). However, a larger RCT involving ICU patients found that there was no statistically significant difference of INR corrections between two FFP dose groups (20.00 ml kg-1 vs. 12.00 ml kg-1) (30). Stanworth et al. (2011) conducted the prospective observational study on national FFP usage among the critically ill, coagulopathy patients. However, there was no significant association between the INR changes with FFP dose (p-value of 0.86) (2).

From the present study findings, it is important for clinicians and blood transfusion services to improvise the prophylactic FFP transfusion practices. The pretransfusion INR threshold shall be practised based on current evidence and supported by previous studies. The biological half-life of procoagulants (protein) in FFP should be considered prior FFP transfusions. If correction of the INR is justified or truly required before interventional procedures, the FFP should be infused shortly before the procedure for the benefit to be incurred at the time of haemostatic challenge. Besides, an adequate dose of FFP shall be calculated in order to provide optimum haemostasis in patients with coagulation factors deficiency (coagulopathy).

CONCLUSION

In conclusion, this study shows that the proportion posttransfusion INR values corrected to less than 1.51

prior to interventional procedures was 33.30%. This includes a patient who achieved complete normalisation of INR. The majority of patients underwent the interventional procedures with posttransfusion INR values of above 1.50 (52 patients) without any bleeding episode documented. This finding was supported the previous evidences that the interventional procedures were safely carried out without complete normalisation of INR (uncorrected INR). In line with others studies, the bleeding incidences were low in the most of procedures and prophylactic transfusions were not indicated. The risk of bleeding can be minimised by the clinicians with proper and skilled procedure techniques. This is in turn, will not expose the patient to transfusion risks. The INR difference showed a significant, positive correlation with pretransfusion INR values and FFP doses. Our data support the need for more clinical research to improve the current understanding of the risk-to-benefit profile of FFP therapy. The FFP transfusion can be avoided for stable, non-bleeding coagulopathy patients especially with mildly elevated INR (INR < 2.0). Not all cases required and benefited to give prophylactic FFP transfusions prior to interventional procedures.

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